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INTL RES & DEVELOP CORP

Document Title
INITIAL SUBMISSION: ACUTE INHALATION TOXICITY STUDY OF METHLENEBIS(4-PHENYL ISOCYANATE) AND 4,4'-DIPHENYLMETHANE DIISOCYANATE IN THE MALE RAT WITH COVER LETTER DATED 10/16/92

Chemical Category
METHYLENEBIS (4-PHENYL ISOCYANATE), 4,4'-DIPHENYLMETHANE DI*

8(e)

CAP

12358

(COMPLIANCE AUDIT PROGRAM)

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Environmental Protection Agency
401 M Street., S.W.
Washington, D.C. 20460
Attn: Section 8(e) Coordinator (CAP Agreement)

Dear Coordinator:

8ECAP-0025

On behalf of the Regulatee and pursuant to Unit II B.1.b. and Unit II C of the 5/28/91CAP Agreement, E.I. Du Pont de Nemours and Co. hereby submits (*in triplicate*) the attached studies. Submission of this information is voluntary and is occasioned by unilateral changes in EPA's standard as to what EPA now considers as reportable information. Regulatee's submission of information is made solely in response to the new EPA §8(e) reporting standards and is not an admission: (1) of TSCA violation or liability; (2) that Regulatee's activities with the study compounds reasonably support a conclusion of substantial health or environmental risk or (3) that the studies themselves reasonably support a conclusion of substantial health or environmental risk.

The "Reporting Guide" creates new TSCA 8(e) reporting criteria which were not previously announced by EPA in its 1978 Statement of Interpretation and Enforcement Policy, 43 Fed Reg 11110 (March 16, 1978). The "Reporting Guide states criteria which expands upon and conflicts with the 1978 Statement of Interpretation. Absent amendment of the Statement of Interpretation, the informal issuance of the "Reporting Guide" raises significant due processes issues and clouds the appropriate reporting standard by which regulated persons can assure TSCA Section 8(c) compliance.

For Regulatee,

Mark H. Christman
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ATTACHMENT 1

Submission of information is made under the 6/28/91 CAP Agreement, Unit II. This submission is made voluntarily and is occasioned by recent changes in EPA's TSCA §8(e) reporting standard; such changes made, for the first time in 1991 and 1992 without prior notice and in violation of Regulatee's constitutional due process rights. Regulatee's submission of information under this changed standard is not a waiver of its due process rights; an admission of TSCA violation or liability, or an admission that Regulatee's activities with the study compounds reasonably support a conclusion of substantial risk to health or to the environment. Regulatee has historically relied in good faith upon the 1978 Statement of Interpretation and Enforcement Policy criteria for determining whether study information is reportable under TSCA §8(e), 43 Fed Reg 11110 (March 16, 1978). EPA has not, to date, amended this Statement of Interpretation.

After CAP registration, EPA provided the Regulatee the June 1, 1991 "TSCA Section 8(e) Reporting Guide". This "Guide" has been further amended by EPA, EPA letter, April 10, 1992. EPA has not indicated that the "Reporting Guide" or the April 1992 amendment supersedes the 1978 Statement of Interpretation. The "Reporting Guide" and April 1992 amendment substantively lowers the Statement of Interpretation 's TSCA §8(e) reporting standard[2]. This is particularly troublesome as the "Reporting Guide" states criteria, applied retroactively, which expands upon and conflicts with the Statement of Interpretation.[3] Absent amendment of the Statement of Interpretation, the informal issuance of the "Reporting Guide" and the April 1992 amendment clouds the appropriate standard by which regulated persons must assess information for purposes of TSCA §8(e).

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[2]In sharp contrast to the Agency's 1977 and 1978 actions to soliciting public comment on the proposed and final §8(e) Policy, EPA has unilaterally pronounced §8(e) substantive reporting criteria in the 1991 Section 8(e) Guide without public notice and comment, See 42 Fed Reg 45362 (9/9/77), "Notification of Substantial Risk under Section 8(e): Proposed Guidance".

[3]A comparison of the 1978 Statement of Interpretation and the 1992 "Reporting Guide" is a appended.

Throughout the CAP, EPA has mischaracterized the 1991 guidance as reflecting "longstanding" EPA policy concerning the standards by which toxicity information should be reviewed for purposes of §8(e) compliance. Regulatee recognizes that experience with the 1978 Statement of Interpretation may cause a review of its criteri. Regulatee supports and has no objection to the Agency's amending reporting criteria *provided that* such amendment is not applied to the regulated community in an unfair way. However, with the unilateral announcement of the CAP under the auspices of an OCM enforcement proceeding, EPA has wrought a terrific unfairness since much of the criteria EPA has espoused in the June 1991 Reporting Guide and in the Agency's April 2, 1992 amendment is new criteria which does not exist in the 1978 Statement of Interpretation and Enforcement Policy.

The following examples of new criteria contained in the "Reporting Guide" that is not contained in the Statement of Interpretation follow:

- o even though EPA expressly disclaims each "status report" as being preliminary evaluations that should not be regarded as final EPA policy or intent[4], the "Reporting Guide" gives the "status reports" great weight as "sound and adequate basis" from which to determine mandatory reporting obligations. ("Guide" at page 20).
- o the "Reporting Guide" contains a matrix that establishes new numerical reporting "cutoff" concentrations for acute lethality information ("Guide" at p. 31). Neither this matrix nor the cutoff values therein are contained in the Statement of Interpretation. The regulated community was not made aware of these cutoff values prior to issuance of the "Reporting Guide" in June, 1991.
- othe "Reporting Guide" states new specific definitional criteria with which the Agency, for the first time, defines as 'distinguishable neurotoxicological effects'; such criteria/guidance not expressed in the 1978 Statement of Interpretation.[5];

- othe "Reporting Guide" provides new review/ reporting criteria for irritation and sensitization studies; such criteria not previously found in the 1978 Statement of Interpretation/Enforcement Policy.
- othe "Reporting Guide" publicizes certain EPA Q/A criteria issued to the Monsanto Co. in 1989 which are not in the Statement of Interpretation; have never been published in the Federal Register or distributed by the EPA to the Regulatee. Such Q/A establishes new reporting criteria not previously found in the 1978 Statement of Interpretation/Enforcement Policy .

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[4]The 'status reports' address the significance, if any, of particular information reported to the Agency, rather than stating EPA's interpretation of §8(e) reporting criteria. In the infrequent instances in which the status reports contain discussion of reportability, the analysis is invariably quite limited, without substantial supporting scientific or legal rationale.

[5] *See, e.g,* 10/2/91 letter from Du Pont to EPA regarding the definition of 'serious and prolonged effects' as this term may relate to transient anesthetic effects observed at lethal levels; 10/1/91 letter from the American Petroleum Institute to EPA regarding clarification of the Reporting Guide criteria.

In discharging its responsibilities, an administrative agency must give the regulated community fair and adequate warning to as what constitutes noncompliance for which penalties may be assessed.

> Among the myriad applications of the due process clause is the fundamental principle that statutes and regulations which purport to govern conduct must give an adequate warning of what they command or forbid.... Even a regulation which governs purely economic or commercial activities, if its violation can engender penalties, must be so framed as to provide a constitutionally adequate warning to those whose activities are governed.

Diebold, Inc. v. Marshall, 585 F.2d 1327, 1335-36 (D.C. Cir. 1978). *See also*, Rollins Environemntal Services (NJ) Inc. v. U.S. Environmental Protection Agency, 937 F. 2d 649 (D.C. Cir. 1991).

While neither the are rules, This principle has been applied to hold that agency 'clarification', such as the Statement of Interpretation, the "Reporting Guide" nor the April 1992 amendments will not applied retroactively.

> ...a federal court will not retroactively apply an unforeseeable interpretation of an administrative regulation to the detriment of a regulated party on the theory that the post hoc interpretation asserted by the Agency is generally consistent with the policies underlying the Agency's regulatory program, when the semantic meaning of the regulations, as previously drafted and construed by the appropriate agency, does not support the interpretation which that agency urges upon the court.

Standard Oil Co. v. Federal Energy Administration, 453 F. Supp. 203, 240 (N.D. Ohio 1978), aff'd sub nom. Standard Oil Co. v. Department of Energy, 596 F.2d 1029 (Em. App. 1978):

The 1978 Statement of Interpretation does not provide adequate notice of, and indeed conflicts with, the Agency's current position at §8(e) requires reporting of all 'positive' toxicological findings without regard to an assessment of their relevance to human health. In accordance with the statute, EPA's 1978 Statement of Interpretation requires the regulated community to use scientific judgment to evaluate the significance of toxicological findings and to determining whether they reasonably support a conclusion of a substantial risk. Part V of the Statement of Interpretation urges persons to consider "the fact or probability" of an effect's occurrence. Similarly, the 1978 Statement of Interpretation stresses that an animal study is reportable only when "it contains reliable evidence ascribing the effect to the chemical." 43 Fed Reg. at 11112. Moreover, EPA's Statement of Interpretation defines the substantiality of risk as a function of both the seriousness of the effect and the probability of its occurrence. 43 Fed Reg 11110 (1978). Earlier Agency interpretation also emphasized the "substantial" nature of a §8(e) determination. See 42 Fed Reg 45362, 45363

(1977). [Section 8(e) findings require "extraordinary exposure to a chemical substance...which critically imperil human health or the environment"].

The recently issued "Reporting Guide" and April 1992 Amendment guidance requires reporting beyond and inconsistent with that required by the Statement of Interpretation. Given the statute and the Statement of Interpretation's explicit focus on substantial human or environmental risk, whether a substance poses a "substantial risk" of injury requires the application of scientific judgment to the available data on a case-by-case basis.

If an overall weight-of-evidence analysis indicates that this classification is unwarranted, reporting should be unnecessary under §8(e) because the available data will not "reasonably support the conclusion" that the chemical presents a substantial risk of serious adverse consequences to human health.

Neither the legislative history of §8(e) nor the plain meaning of the statute support EPA's recent lowering of the reporting threshold that TSCA §8(e) was intended to be a sweeping information gathering mechanism. In introducing the new version of the toxic substances legislation, Representative Eckhart included for the record discussion of the specific changes from the version of H. R. 10318 reported by the Consumer Protection and Finance Subcommittee in December 1975. One of these changes was to modify the standard for reporting under §8(e). The standard in the House version was changed from "causes or contributes to an unreasonable risk" to "causes or significantly contributes to a substantial risk". This particular change was one of several made in TSCA §8 to avoid placing an undue burden on the regulated community. The final changes to focus the scope of Section 8(e) were made in the version reported by the Conference Committee.

The word "substantial" means "considerable in importance, value, degree, amount or extent". Therefore, as generally understood, a "substantial risk" is one which will affect a considerable number of people or portion of the environment, will cause serious injury and is based on reasonably sound scientific analysis or data. Support for the interpretation can be found in a similar provision in the Consumer Product Safety Act. Section 15 of the CPSA defines a "substantial product hazard" to be:

> "a product defect which because of the pattern of defect, the number of defective products distributed in commerce, the severity of the risk, or otherwise, creates a substantial risk of injury to the public."

Similarly, EPA has interpreted the word 'substantial' as a quantitative measurement. Thus, a 'substantial risk' is a risk that can be quantified. *See,* 56 Fed Reg 32292, 32297 (7/15/91). Finally, since information pertinent to the exposure of humans or the environment to chemical substances or mixtures may be obtained by EPA through Sections 8(a) and 8(d) regardless of the degree of potential risk, §8(e) has specialized function. Consequently, information subject to §8(e) reporting should be of a type which would lead a reasonable man to conclude that some type action was required immediately to prevent injury to health or the environment.

Attachment

Comparison:

Reporting triggers found in the 19[illegible] "Statement of Interpretation/ Enforcement Policy",43 Fed Reg 11110 (3/16/78) and the June 1991 *Section 8(e) Guide.*

TEST TYPE	1978 POLICY CRITERIA EXIST?	New 1991 GUIDE CRITERIA EXIST?
ACUTE LETHALITY		
Oral	N}	Y}
Dermal	N}	Y}
Inhalation (Vapors)	}[6]	}[7]
aerosol	N}	Y}
dusts/ particles	N}	Y}
SKIN IRRITATION	N	Y[8]
SKIN SENSITIZATION (ANIMALS)	N	Y[9]
EYE IRRITATION	N	Y[10]
SUBCHRONIC (ORAL/DERMAL/INHALATION)	N	Y[11]
REPRODUCTION STUDY	N	Y[12]
DEVELOPMENTAL TOX	Y[13]	Y[14]

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[6] 43 Fed Reg at 11114, comment 14:

"This policy statements directs the reporitng of specifiec effects when unkn[illegible]o the Administrator. Many routine tests are based on a knowledge of toxicity a[illegible]d with a chemicalL unknown effects occurring during such a range test may have to be repo.ted if they are those of concern tot he Agency and if the information meets the criteria set forth in Parts V and VII."

[7] Guide at pp.22, 29-31.

[8] Guide at pp-34-36.

[9] Guide at pp-34-36.

[10] Guide at pp-34-36.

[11] Guide at pp-22; 36-37.

[12] Guide at pp-22

[13] 43 Fed Reg at 11112

"Birth Defects" listed.

[14] Guide at pp-22

NEUROTOXICITY	N	Y[15]
CARCINOGENICITY	Y[16]	Y[17]
MUTAGENICITY		
In Vitro	Y}[18]	Y} [19]
In Vivo	Y}	Y}
ENVIRONMENTAL		
Bioaccumulation	Y}	N
Bioconcentration	Y}[20]	N
Oct/water Part. Coeff.	Y}	N
Acute Fish	N	N
Acute Daphnia	N	N
Subchronic Fish	N	N
Subchronic Daphnia	N	N
Chronic Fish	N	N
AVIAN		
Acute	N	N
Reproductive	N	N
Reprodcutive	N	N

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[15] Guide at pp-22, 33-34

[16] 43 Fed Reg at 11112
"Cancer" listed

[17] Guide at pp-21.

[18] 43 Fed Reg at 11112; 11115 at Comment 15
"Mutagenicity" listed/ *in vivo* vs *invitro* discussed; discussion of "Ames test".

[19] Guide at pp-23.

[20] 43 Fed Reg at 11112: 11115 at Comment 16.

CAS # 9016-87-9 and 101-68-8
Chem: Methylenebis (4-phenyl isocyanate) and 4,4'-diphenylmethane diisocyanate
Title: Acute Inhalation Toxicity LC50 in the Male Albino Rat
Date: 1-29-65
Summary of Effects: Highly toxic

SPONSOR: The Upjohn Company

COMPOUNDS: PAPI
MDI, Pure, Distilled

SUBJECT: Acute Inhalation Toxicity (LC_{50}) in the Male Albino Rat.

Francis X. Wazeter, Ph.D.
Director of Research
International Research and
Development Corporation

Collaborators:

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R. G. Geil, D.V.M., Director of Pathology
R. T. Jacobs, D.V.M., Toxicologist

Date: January 29, 1965

203-004

I. SYNOPSIS

The test compounds were examined for acute inhalation toxicity (LC_{50}) using the male albino rat. All compounds were tested in the vapor form. Six rats for every concentration of each respective test agent were used.

An LC_{50} for PAPI could not be determined, since the physical constants of PAPI and the experimental protocol did not permit such a calculation.

While lethal levels were established for MDI, Pure, Distilled, an exact LC_{50} could not be calculated from the data. The approximate LC_{50} lies between 172 and 187 mg./L.

International Research and Development Corporation

II. COMPOUNDS

The test compounds were received from the Upjohn Company, Carwin Division, North Haven, Connecticut, on August 24 and December 24, 1964.

Each of the four test compounds was sealed in a glass bottle and was identified as follows:

Compound	Code No.	Description
PAPI	2B-14-65	Dark brown viscous liquid
MDI, Pure, Distilled	---	Pale orange moist crystals

III. METHODS

A. General Procedure:

Male, albino rats of the Spartan Sprague-Dawley strain and weighing from 200 to 300 grams were used. The rats were individually housed in wire mesh cages elevated above the droppings and maintained in air-conditioned and humidity-controlled quarters throughout the pre-exposure and post-exposure periods. Food and water were available ad libitum except during the exposure period.

Body weights on all animals used were obtained prior to exposure to each respective agent and at 7 and 14 days after exposure.

All of the rats were observed for evidence of pharmacodynamic and/or toxic signs during the exposure period; for an additional period of several hours immediately after exposure; and daily for 13 days thereafter.

Animals which failed to survive the post-exposure observation period were necropsied and examined. All rats which survived to the termination of the 14-day observation period were sacrificed by means of an intraperitoneal injection of sodium pentobarbital and also necropsied and examined.

B. Compound Administration:

All of the compounds in these tests were analyzed in vapor form. This was accomplished by heating each respective compound in a flask on a water or oil bath at the desired temperature to produce vapors.

The vapors thus formed were carried into the exposure chamber containing the rats by use of an air source produced by a compressor. Prior to entrance into the evaporating flask containing the test agent, the air was passed through a glass wool filter and two drying tubes containing calcium chloride to clean and dry it.

The concentration of the vapors of each test agent carried by the inflowing air could be varied either by changing the volume of the inflow of air, or by altering the temperature of the bath producing the vapors, or as in the case of PAPI , by altering the speed of infusion of the test materials into the evaporating chamber with an infusion pump. Upon occasion, a second air source was introduced into the line carrying the vapors of a given agent into the exposure chamber to aid in further controlling the concentration of a given test material.

The rats were divided into groups of six animals each. One group was used at each respective concentration of each test agent analyzed.

For exposure purposes, a nine-liter air-tight chamber was used. All animals were exposed for one continuous hour to the vapors of each respective test agent.

1. PAPI:

This agent was injected into the distillation flask with a Harvard Infusion Pump (Model No. 600-910). The distillation flask was heated to a temperature of approximately 150 ± 2° Centigrade with an oil bath. The vapors thus formed were carried into the exposure chamber with a controlled inflow of air, as previously described, at 10 liters per minute..

Two groups of six rats each were thus exposed to analyzed concentrations of PAPI of 14.7 or 17.0 micrograms per liter (mcg./L.). Higher concentrations of PAPI could not be obtained by increasing the inflow of the compound with the infusion pump, and the degree of heat used could not be increased without exceeding the decomposition temperature of the agent. Furthermore, reduction of airflow produced

condensation (fallout) within the exposure chamber. Thus, only two concentrations of PAPI were analyzed.

The table below describes the experimental variables used in this test.

PAPI

Experimental Variables:

Infusion Speed ml./min.	Oil Bath Temp. °C.	Airflow (L/M)	Analyzed Exposure Chamber Concen. (mcg./L.)
0.194	150	10	14.7
0.494	150	10	17.0

2. MDI, Pure, Distilled:

MDI, Pure, Distilled was evaluated at analyzed concentrations of 0.6, 80.8, 162.0, 171.5, 186.6, 562,5 and 1530 mcg./L., using 6 rats at each respective concentration.

The vapor for the lowest concentration analyzed (0.6 mcg./L.) was produced by passing air through the test agent which was contained in a flask on an oil bath. The oil bath was maintained at a temperature of 100 ± 2° C. The airflow into the evaporating chamber was passed directly into the exposure chamber at a speed of one liter per minute.

All succeeding concentrations were produced in a similar manner, except that the test agent was heated to a temperature of approximately 200 ± 2° C. Airflow through the evaporating chamber was varied between 1 and 2 liters per minute. Further dilution of the air containing the vapors was accomplished with a second air source which was interposed into the system just prior to its entry

into the exposure chamber. Airflow from this second source was varied from 0 to 10 liters per minute. By varying the airflow from the second source, the concentration of the vapors entering the exposure chamber could be controlled. The following table describes the experimental variables and the concentrations of MDI thus produced.

MDI, Pure, Distilled

Experimental Variables:

Oil Bath Temp. °C.	Airflow (Liters/Minute) Primary Source	Secondary Source	Total	Analyzed Exposure Chamber Concen. (mcg./L.)
100	1.0	0.0	1.0	0.6
200	1.0	10.0	11.0	80.8
200	1.5	7.0	8.5	162.0
200	1.0	6.0	7.0	171.5
200	1.5	6.0	7.5	186.6
200	2.0	2.0	4.0	562.5
200	2.0	0.0	2.0	1530.0

C. Analytical Methods

Prior to the exposure of the animals to varying concentrations of each test agent, calibration curves were prepared for each substance by the following method: Serial dilution of a known concentration of each respective test agent in the reagent (0.5 per cent p-dimethylaminobenzaldehyde in 50 per cent glacial acetic acid) were prepared. After maximum color development had occurred, each dilution was read in a Coleman spectrophotometer at a wave length of 425 millimicrons, using a reagent blank to balance the instrument.

The optical densities thus obtained were plotted against the concentrations in mcg./ml. for each test agent. The resultant curves obtained were used to determine the concentration in mcg./L. of subsequently obtained samples of atmospheric concentrations from the exposure chamber of each agent during a given exposure.

IV. RESULTS

A. Pharmacodynamic and/or Toxic Signs:

1. PAPI:

a. 14.7 and 17.0 mcg./L.:

All rats at both concentrations of PAPI appeared essentially normal throughout the one-hour exposure period and the 14-day post-exposure observation period. Slight salivation and erythema were observed during the exposure period in both groups of rats. All rats at both concentrations used survived the 14-day observation period.

2. MDI, Pure, Distilled:

a. 0.6 mcg./L.:

Signs seen during the exposure included a general slight erythema and restlessness. Five-of-six exhibited slight salivation and 2-of-6 showed slight nasal porphyrin discharge. All rats in this group appeared normal the following day and remained so until necropsy.

b. 80.8 mcg./L.:

During the exposure the rats exhibited salivation, excessive lacrimation and clear nasal drip, dyspnea, escape behavior, and slight nasal porphyrin discharge. No signs were seen from the day following the exposure until necropsy. All rats survived the 14-day observation period.

c. 162 mcg./L.:

Signs seen during this exposure were similar to those seen at the 80.8 mcg./liter level, but appeared among the rats much earlier, and were more marked at the termination of the exposure. Again, all 6 rats appeared essentially normal

from the day following the exposure until necropsy and all survived the observation period.

d. 171.5 mcg./L.:

Signs recorded during this exposure included those noted above at lower concentrations, plus a slight increase in activity during the initial few minutes. One-of-six rats showed marked nasal porphyrin at the termination of the exposure. All rats appeared essentially normal from the day following the exposure until necropsy and all survived to termination of the test period.

e. 186.6 mcg./L.:

In addition to the salivation, excessive lacrimation, clear nasal drip, and dyspnea, previously mentioned, an increase in grooming activity, and eye-squint were seen during this exposure. At the termination of this exposure, all rats exhibited salivation and dyspnea, and 3-of-6 showed muscle flaccidity. Three-of-six rats died overnight after the exposure. The day following the exposure, 1-of-3 showed dyspnea and nasal and ocular porphyrin, and 2-of-3 showed hypoactivity. The 4th mortality occurred 26 hours after the exposure. From the 2nd post-exposure day on, the 2 survivors appeared essentially normal.

f. 562.5 mcg./L.:

Within 10 minutes after initiating this exposure, the exposure chamber was completely filled with "fog". Marked ptyalism, dyspnea, eye-squint, excessive lacrimation, and increased grooming were recorded. In addition, after 55 minutes, the eyes appeared dark and the exposed skin (ears and paws) appeared cyanotic. Inspection of the rats immediately after the exposure revealed

dyspnea, salivation and cyanosis, all of which lasted throughout the balance of the day. Six-of-six mortalities occurred overnight.

g. 1530.0 mcg./L.:

During this exposure, the test chamber again became filled with "fog" during the first few minutes. Gross observations were similar to those recorded for the 562.5 level. Eye-squint advanced to eye-closure and the dark appearance of the eyes and the cyanotic condition of the exposed skin was seen during exposure and at termination of the exposure period. Three-of-six died during the exposure, and the remaining 3 rats within one hour thereafter.

B. Body Weights (Table 2):

1. PAPI:

Rats exposed to an analyzed atmospheric concentration of PAPI of 14.7 mcg./L. showed essentially normal body weight gains. Those rats at the 17.0 mcg./L. level showed a very slight inhibition of body weight gain during the first week only.

2. MDI, Pure, Distilled:

Rats exposed to an analyzed concentration of 0.6 mcg./L. of MDI, Pure, Distilled, showed normal body weight gain during the 2-week period of observation. However, the average body weight gain for the surviving rats of the other 6 groups exposed to the vapors of this agent appeared to be inhibited for the first week.

C. Necropsy Examination

1. Mortalities:

Necropsies made on those rats that died during the 2-week period of observation revealed the following:

a. PAPI:

No Mortalities.

b. MDI, Pure, Distilled:

(1) 186.6 mcg./L.: Four-of-four exhibited hydrothorax and lungs with edema and congestion; 1-of-4, lungs with severe hemorrhages.

(2) 562.5 mcg./L.: Six-of-six showed hydrothorax and lungs with generalized congestion and edema.

(3) 1520.0 mcg./L.: Six-of-six showed lungs with severe generalized hemorrhage and edema throughout.

2. Survivors:

Necropsies made on those rats which survived the 2-week period of observation revealed the following:

a. PAPI:

(1) 14.7 mcg./L.: Four-of-six, no gross lesions; 1-of-6, lung with 2 mm. dark area; 1-of-6, lungs with 6 mm. areas of congestion.

(2) 17.0 mcg./L.: Four-of-six, no gross lesions; 2-of-6, lungs with 6-10 mm. areas of congestion.

b. MDI, Pure, Distilled:

(1) 0.6 mcg./L.: Four-of-six, no gross lesions; 2-of-6, lungs with 10 mm. areas of congestion.

(2) 80.8 mcg./L.: Five-of-six, no gross lesions; 1-of-6, lung with 6-15 mm. areas of hyperemia.

(3) 162 mcg./L.: One-of-six, no gross lesions; 2-of-6, lungs with 2 mm. red foci; 1-of-6, lungs with two 6 mm. areas of congestion.

(4) 171.5 mcg./L.: No gross lesions seen.

(5) 186.6 mcg./L.: One-of-two, no gross lesions; and 1-of-2, a lung with a 2 mm. red foci.

D. Acute Inhalation Toxicity (LC_{50}):

1. PAPI:

It was not possible to achieve an LC_{50} for PAPI.

2. MDI, Pure, Distilled:

Data obtained from the exposures of 7 groups of 6 rats each to 7 different analyzed atmospheric concentrations of MDI, Pure, Distilled vapors does not permit the calculation of an LC_{50}. However, inspection of the levels employed and the mortalities obtained reveals that the LC_{50} is approximately 178 mcg./L.

E. Analytical Results:

The analysis of the actual chamber concentrations of the agents used in these studies at the various concentrations employed were obtained by interpolation from the values appearing in Table 1. In actual practice, graphs were constructed for each individual agent by plotting the data appearing in Table 1. Actual concentrations in the exposure chamber were calculated by obtaining optical densities of 425 millimicrons as previously described under methods, entering the table at the respective density obtained and reading the concentration indicated.

Acute Inhalation Toxicity Studies in the Rat.

TABLE 1. Calibration Curves.

Compound	Optical Densities: 0.05	0.10	0.15	0.20	0.25	0.30	0.35	0.40	0.45	0.50	0.55	0.60	0.65	0.70	0.75	0.80	0.85
	Concentration, mcg./ml.																
PAPI	0.3[illegible]	0.53	0.75	1.00	1.27	1.50	1.77	2.00	2.26	2.54	2.90	3.30	3.77	4.37	5.25	6.20	-
MDI, Pure	0.10	0.19	0.30	0.40	0.53	0.62	0.77	0.90	1.04	1.22	1.40	1.58	1.77	2.00	2.35	3.00	4.25

Acute Inhalation Toxicity Studies in the Rat.

TABLE 2. Average Body Weights, Grams.

Test Compound Concentration (mcg./L.)	Control	7 Days	14 Days
PAPI:			
14.7	217	271	301
17.0	261	274	304
MDI, Pure, Distilled:			
0.6	223	279	303
80.8	273	277	323
162.0	263	282	319
171.5	272	274	323
186.6	268	259[a]	305[a]
562.5	292	-	-
1530.0	289	-	-

a - 2 rats only

Acute Inhalation Toxicity Studies in the Rat.

TABLE 3. Mortality Data in the Male Albino Rat.

Analyzed Atmospheric Concentration mcg./L..	Time of Death - Days Post-Exposure No. Died/No. Exposed																LC50 and Confidence Limits (mcg./L.)
	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	Total	
PAPI:																	
14.7																0/6	None
17.0																0/6	Possible
MDI, Pure:																	
0.6																0/6	
80.8																0/6	
162.0																0/6	Approximately
171.5																0/6	178
186.6	3/6	1/3														4/6	
562.5	6/6															6/6	
1530.0	6/6															6/6	

CERTIFICATE OF AUTHENTICITY

THIS IS TO CERTIFY that the microimages appearing on this microfiche are accurate and complete reproductions of the records of U.S. Environmental Protection Agency documents as delivered in the regular course of business for microfilming.

Date produced 6 (Month) 24 (Day) 96 (Year) Marcia Tubolino Camera Operator

Place Syracuse (City) New York (State)

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